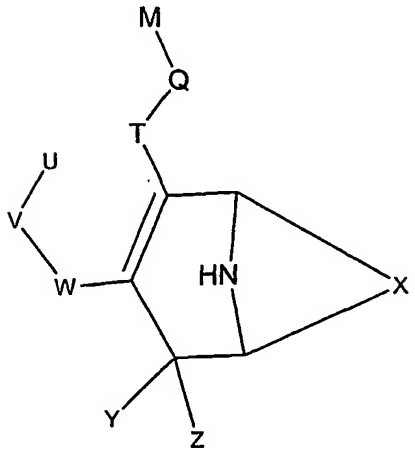
Claims

1. Compounds of the general formula I



Formula I

wherein

Y and Z represent independently from each other hydrogen, fluorine or a methyl group, or Y and Z may together form a cyclopropyl ring;

X represents $-CH_2-CH(K)-CH_2-$; $-CH_2CH_2-$; $-CH_2OCH_2-$; $-CH_2SCH_2-$; $-CH_2SOCH_2-$; $-CH_2SO_2CH_2-$; -CO-NL-CHR^6-; $-CHR^6$-NL-CO-;

W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

V represents a bond; $-(CH_2)_r-$; -A-$(CH_2)_s-$; $-CH_2$-A-$(CH_2)_t-$; $-(CH_2)_s$-A-; $-(CH_2)_2$-A-$(CH_2)_u-$; -A-$(CH_2)_v$-B-; $-CH_2-CH_2-CH_2$-A-CH_2-; -A-CH_2-CH_2-B-CH_2-; $-CH_2$-A-CH_2-CH_2-B-; $-CH_2-CH_2-CH_2$-A-CH_2-CH_2-; $-CH_2-CH_2-CH_2-CH_2$-A-CH_2-; -A-CH_2-CH_2-B-CH_2-CH_2-; $-CH_2$-A-CH_2-CH_2-B-CH_2-; $-CH_2$-A-$CH_2-CH_2-CH_2$-B-;

$-CH_2-CH_2$-A-CH_2-CH_2-B-; –O-CH_2-$CH(OCH_3)$-CH_2-O; -O-CH_2-$CH(CH_3)$-CH_2-O-; -O-CH_2-$CH(CF_3)$-CH_2-O-; -O-CH_2-$C(CH_3)_2$-CH_2-O-; -O-CH_2-$C(CH_3)_2$-O-; -O-$C(CH_3)_2$-CH_2-O-; -O-CH_2-$CH(CH_3)$-O-; -O-$CH(CH_3)$-CH_2-O-; -O-CH_2-$C(CH_2CH_2)$-O-; -O-$C(CH_2CH_2)$-CH_2-O-;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^5$; heteroaryl-$O(CH_2)_vR^5$; aryl-$O(CH_2)_2O(CH_2)_wR^5$; heteroaryl-$(CH_2)_2O(CH_2)_wR^5$;

L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$; $-COCH(Aryl)_2$;

K represents –H; $-CH_2OR^3$; $-CH_2NR^2R^3$; $-CH_2NR^2COR^3$; $-CH_2NR^2SO_2R^3$; $-CO_2R^3$; $-CH_2OCONR^2R^3$; $-CONR^2R^3$; $-CH_2NR^2CONR^2R^3$; $-CH_2SO_2NR^2R^3$; $-CH_2SR^3$; $-CH_2SOR^3$; $-CH_2SO_2R^3$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, $-OCOR^2$, $-COOR^2$, lower alkoxy, cyano, $-CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), $-NH(NH)NH_2$, $-NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; $-COOR^2$; $-CONH_2$;

R^5 represents –OH, $-OCOR^2$, $-COOR^2$, $-NR^2R^{2'}$, $-OCONR^2R^{2'}$, $-NCONR^2R^{2'}$, cyano, $-CONR^2R^{2'}$, SO_3H, $-SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), $-NH(NH)NH_2$, $-NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^6 represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be unsubstituted or monosubstituted with hydroxy, $-CONH_2$, -COOH, imidazoyl, $-NH_2$, -CN, $-NH(NH)NH_2$;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 2, 3, or 4;

w is the integer 1 or 2;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

2. Compounds of general formula I according to claim 1 wherein Z, Y, W, V, U, T, Q, and M are as defined in general formula I and

X represents $-CH_2CH_2-$.

3. Compounds of general formula I according to any one of claims 1 to 2 wherein Z, Y, X, W, V, U, T, Q, and M are as defined in general formula I and

L represents H; $-COR^{3''}$; $-COOR^{3''}$; $-CONR^{2''}R^{3''}$;

$R^{2''}$ and $R^{3''}$ represent independently lower alkyl; lower cycloalkyl - lower alkyl, which lower alkyl and lower cycloalkyl-lower alkyl are undubstituted or mono-substituted with halogen, -CN, -OH, $-OCOCH_3$, $-CONH_2$,-COOH, or $-NH_2$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized.

4. Compounds of general formula I according to any one of claims 1 to 3 wherein Z, Y, X, W, V, and U are as defined in general formula I and

T represents $-CONR^1-$;

Q represents methylene;

M represents aryl-$O(CH_2)_vR^5$; heteroaryl-$O(CH_2)_vR^5$.

5. Compounds of general formula I according to any one of claims 1 to 4 wherein Z, Y, V, U, T, Q, and M are as defined in general formula I and

W represents a 4-substituted phenyl.

6. Compounds of general formula I according to any one of claims 1 to 5 wherein Z, Y, X, W, V, Q, T, and M are as defined in general formula I and

U is a mono-, di-, or trisubstituted phenyl whereby the substituents are halogen; lower alkyl or lower alkoxy.

7. Compounds of formula I according to any one of claims 1 to 6 wherein

Z and Y represent hydrogen;

U represents a tri-substituted phenyl ring substituted independently with halogen or C_1-C_4-alkyl;

V represents $-O-CH_2-CH_2-CH_2-$; $-O-CH_2-CH_2-O-$; $-O-CH_2-CH_2-$; $-CH_2-CH_2-O-$; $-O-CH_2-CH_2-CH_2-O-$; $-CH_2-CH_2-CH_2-O-$;

W represents a phenyl ring substituted by V in the 4-position and connected to the carbon atom at the double bond of the tetrahydro-pyridin ring in the 1-position;

X represents $-CH_2-CH_2-$; $-CH_2-SO-CH_2-$; $-CH_2-SO_2-CH_2-$; $-CH_2-O-CH_2-$;

T represents $-CONR^1-$, wherein R^1 is a cycloalkyl group;

Q represents $-CH_2-$;

M represents a substituted pyridyl-$O(CH_2)_vR^5$ group substituted with C_1-C_4-alkyl, wherein R^5 is hydroxyl; $-COOR_2$, wherein R^2 is hydrogen or C_1-C_4-alkyl; or $-CONR^2R^{2'}$, wherein R^2 and $R^{2'}$ are hydrogen or C_1-C_4-alkyl.

8. Compounds of formula I according to any one of claims 1 to 7 wherein

Z and Y represent hydrogen;

U represents a tri-substituted phenyl ring substituted independently with halogen or a phenyl ring substituted in 2- and 6- position with chloro and in 4-position with a methyl group;

V represents $-O-CH_2-CH_2-CH_2-$; $-O-CH_2-CH_2-O-$;

W represents a phenyl ring substituted by V in the 4-position and connected to the carbon atom at the double bond of the tetrahydro-pyridin ring in the 1-position;

X represents $-CH_2-CH_2-$; $-CH_2-SO_2-CH_2-$; $-CH_2-O-CH_2-$;

T represents $-CONR^1-$, wherein R^1 is a cyclopropyl group;

Q represents $-CH_2-$;

M represents a pyridinyl-$O(CH_2)_vR^5$ group, whereby the pyridinyl ring is substituted with a methyl group, wherein R^5 represents hydroxyl; or $-COOR_2$, wherein R^2 is hydrogen or methyl; or R^5 is $-CONH_2$ and v is the integer 2 or 3.

9. The compounds according to any one of claims 1 - 8 selected from the group consisting of

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide,

(*rac.*)-(*1R**, *5S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide,

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,3-dioxo-3λ^6-thia-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide,

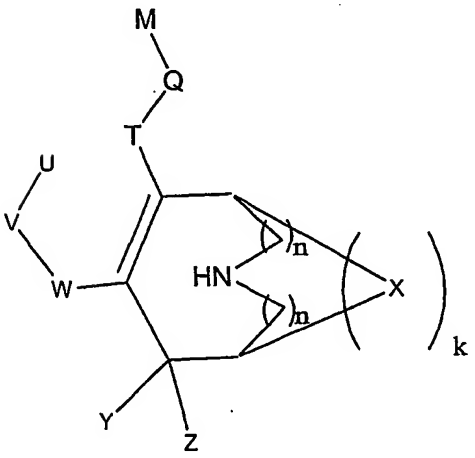
(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3-oxa-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide,

(*rac.*)-(*1R**, *5S**)-3-(4-{[(3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carbonyl)cyclopropylamino]methyl}-3-methyl-pyridin-2-yloxy)propionic acid,

(*rac.*)-(*1R**, *5S**)-3-(4-{[(3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carbonyl)cyclopropylamino]methyl}-3-methyl-pyridin-2-yloxy)propionic acid methyl ester, and

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid [2-(2-carbamoylethoxy)-3-methyl-pyridin-4-ylmethyl]cyclopropylamide.

10. Compounds of the general formula **I**



Formula **I**

wherein

Y and Z represent independently from each other hydrogen, fluorine or a methyl group, or Y and Z may together form a cyclopropyl ring; in case k represents the integer 1, Y and Z both represent hydrogen;

X represents $-(CH_2)_m-N(L)-(CH_2)_m-$; $-CH_2-CH(K)-CH_2-$; $-CH_2CH_2-$; $-CH_2OCH_2-$; $-CH_2SCH_2-$; $-CH_2SOCH_2-$; $-CH_2SO_2CH_2-$; $-CO-NL-CO-$; $-CO-NL-CHR^6-$; $-CHR^6-NL-CO-$;

W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

V represents a bond; $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$; $-O-CH_2-CH(OCH_3)-CH_2-O$; $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-CH(CF_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$; $-O-CH_2-C(CH_3)_2-O-$; $-O-C(CH_3)_2-CH_2-O-$; $-O-CH_2-CH(CH_3)-O-$; $-O-CH(CH_3)-CH_2-O-$; $-O-CH_2-C(CH_2CH_2)-O-$; $-O-C(CH_2CH_2)-CH_2-O-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^5$; heteroaryl-$O(CH_2)_vR^5$; aryl-$O(CH_2)_2O(CH_2)_wR^5$; heteroaryl-$(CH_2)_2O(CH_2)_wR^5$;

L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$; $-COCH(Aryl)_2$;

K represents –H; $-CH_2OR^3$; $-CH_2NR^2R^3$; $-CH_2NR^2COR^3$; $-CH_2NR^2SO_2R^3$; $-CO_2R^3$; $-CH_2OCONR^2R^3$; $-CONR^2R^3$; $-CH_2NR^2CONR^2R^3$; $-CH_2SO_2NR^2R^3$; $-CH_2SR^3$; $-CH_2SOR^3$; $-CH_2SO_2R^3$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH^2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

R^5 represents –OH, -$OCOR^2$, -$COOR^2$, -$NR^2R^{2'}$, -$OCONR^2R^{2'}$, -$NCONR^2R^{2'}$, cyano, -$CONR^2R^{2'}$, SO_3H, -$SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^6 represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be unsubstituted or monosubstituted with hydroxy, -$CONH_2$, -COOH, imidazoyl, -NH_2, -CN, -$NH(NH)NH_2$;

k is the integer 0 or 1;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0; in case n represents the integer 1, m is the integer 0; in case k represents the integer 0, n represents the integer 0; in case X does not represent –$(CH_2)_m$-N(L)-$(CH_2)_m$-, n represnts the integer 0;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 2, 3, or 4;

w is th integer 1 or 2;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

11. Pharmaceutical compositions containing a compound of any one of claims 1 - 10 and usual carrier materials and adjuvants for the treatment or prophylaxis of disorders which are associated with a dysregulation of the renin-angiotensin system (RAS), comprising cardiovascular and renal diseases, hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

12. A method for the treatment or prophylaxis of diseases which are related to the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases which are related to the RAS, which method comprises administrating a compound according to any one of claims 1 to 10 to a human being or animal.

13. The use of compounds according to any one of claims 1 to 10 for the treatment or prophylaxis of diseases which are associated with the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

14. The use of one or more compounds of any one of claims 1 to 10 in combination with other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, for the treatment of disorders as set forth in any one of claims 10 to 13.